REMARKS

FORMAL MATTERS:

Claims 16-24, 49-55, and 65-76 are pending after entry of the amendments set forth herein.

Claims 56-64 and 77-82 are canceled without prejudice.

Claims 16 and 49 have been amended. Support for these amendments is found in the specification at, for example, page 17, lines 17-19

No new matter has been added.

REJECTIONS UNDER §112, ¶1 - ENABLEMENT

Item 6 (Office Action, page 3)

Claims 16-24, 49-55, and 65-76 has been rejected under 35 U.S.C. § 112, first paragraph, for allegedly not describing the subject matter in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

In particular, the Office Action asserts that, although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules, the specification does not reasonably provide enablement for inhibiting protein-protein interaction *in vivo* with the non-naturally occurring bifunctional molecules.

In the spirit of expediting prosecution and without conceding as to the correctness of the rejection, the claims have been amended to recite an in vitro utility. Support for the amendment can be found in the claims as originally filed and throughout the specification, at for example, page 17, lines 17-19.

As such, the Applicants respectfully request that this rejection be withdrawn.

Item 7 (Office Action, page 8)

Claims 16-24, 49-55, and 65-76 has been rejected under 35 U.S.C. § 112, first paragraph, for allegedly not describing the subject matter in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. In particular, the Office Action asserts that, although the specification is enabling for the single bifunctional molecule

complex FKBP-NFAT, it does not reasonably provide enablement for the use of any and all bifunctional molecules in the claimed methods. In view of the remarks made below, this rejection is respectfully traversed.

When evaluated in view of the relevant Wands factors[1], the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 16-24, 49-55, and 65-76 contain subject matter which is adequately described in the specification in such a way to teach someone how to make and use the claimed invention without having to practice undue experimentation.

The Applicants maintain that the specification provides ample disclosure for other non-naturally occurring bifunctional inhibitor molecules. For example, the subject non-naturally occurring bifunctional inhibitor molecules are described in general at, for example, on page 4, and with greater detail with respect to the target protein ligand at, for example, page 5, line 1, through page 7, line 3, the blocking protein ligand at, for example, page 7, line 5, though page 11, line 18; the linking moiety at, for example, page 11, line 20, through page 12, line 29; and methods of making the subject bifunctional molecules and methods of screening bifunctional molecules are described at, for example, page 12, line 31, through page 17, line 7. Therefore, in view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, and experimentation that may be necessary is reasonable.

In support, the Applicants note that a research article published after the filing date of the present application, reports successful use of different bifunctional inhibitor molecules synthesized according to the disclosure in the present application and used to inhibit interaction between target and binding proteins. For example, Gestwicki et al., Science 306:865-869 (2004) (Exhibit A), discloses use of the bifunctional inhibitor molecule in preventing interaction and aggregation of β-amyloid (Aβ) peptides generated by proteolytic cleavage of amyloid precursor protein. The authors, which include an inventor of the present application, disclose use of a bifunctional inhibitor molecule comprising a binding molecule that binds FK506 binding protein and a targeting molecule that interacts with aggregating Aβ. The bifunctional inhibitor

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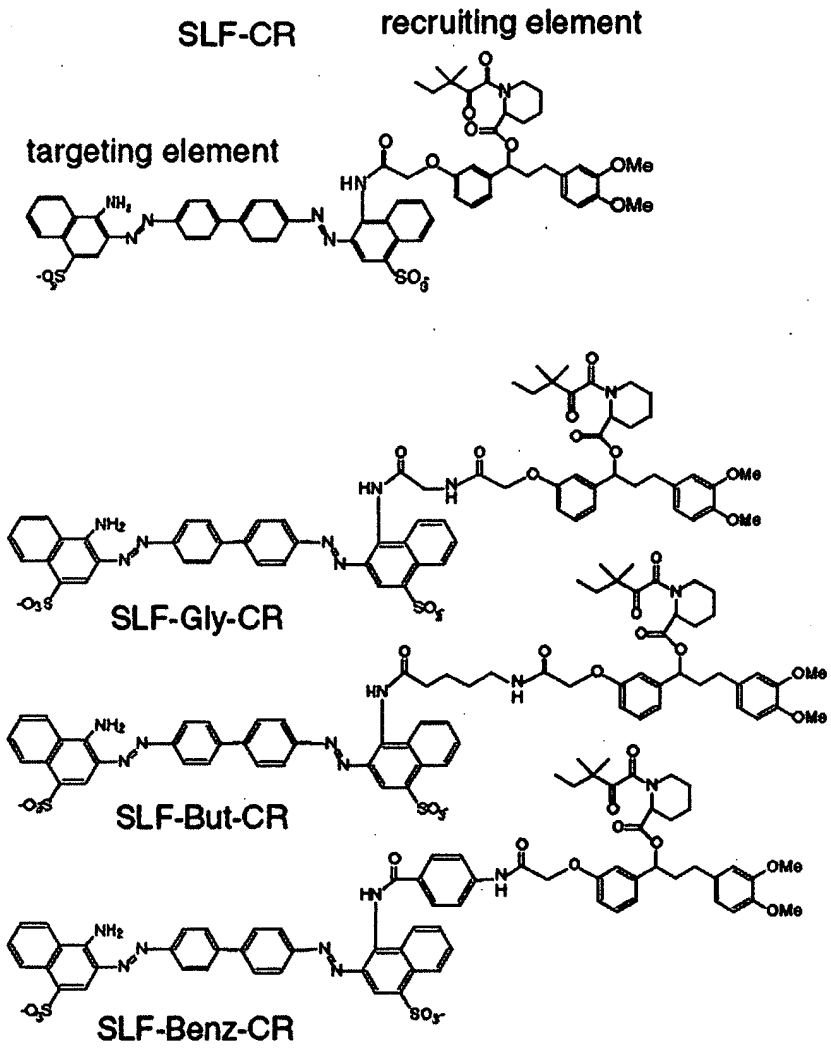
1 (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

molecules include the following four examples that include a SLF (Synthetic ligand for FK506-binding protein) domain as the target protein ligand, CR (Congo Red) as the blocking protein ligand, without a linker and three different examples including linkers (Gly, But, and Benz):



The authors, using the experiments described in the present application, show that application of the four different bifunctional inhibitor molecules to cultured hippocampal neurons results in distinct changes in cellular morphology as well as aggregation and distribution of amyloid fibrils (see page 866, column 3 through page 4 and Figs. 2 and 4). Accordingly, based on the disclosure of the present application, the authors were capable of practicing the

subject invention without undue experimentation using four bifunctional compounds different than the bifunctional molecule complex FKBP-NFAT.

In sum, the Applicants maintain that the amount of experimentation required to practice the subject invention would not be undue and excessive because working examples have been provided, guidance is given on how to generate such compounds, and one of skill in the art would be able to perform the experiments as a matter of routine as exemplified by Gestwicki et al. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the remarks presented herein

The claims pending in the present application are fully enabled by the specification, in view of the description and examples provided therein as well as exemplified by the work reported by Gestwicki et al., as found in Exhibit A to this response. The Applicants have discovered and are claiming a new approach to inhibiting protein-protein interactions, and have enabled this approach with extensive description of the nature of the compounds used and specific representative exemplification. **As demonstrated by the Gestwicki et al. group (Exhibit A), the guidance provided by the Applicants was entirely sufficient to produce four bifunctional molecule different than the FKBP-NFAT of the application that are capable of inhibiting protein-protein interaction between a target protein and binding proteins.** Therefore, there is no reason to think that such a disclosure cannot be extrapolated to the pending claims.

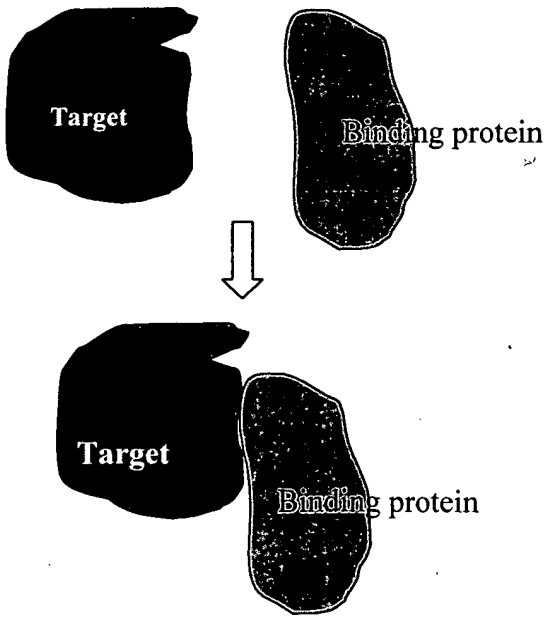
For at least the reasons provided above, the claims are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of under 35 U.S.C. §112, first paragraph be withdrawn.

REJECTIONS UNDER §102

Claims 16-24, 49-55, and 65-76 have been rejected under 35 U.S.C. § 102(a) for allegedly being anticipated by Briesewitz et al., PNAS 96:1953-1958 (1999). In view of the remarks made below, this rejection may be withdrawn.

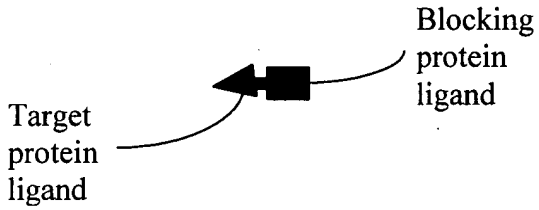
With respect to the pending claims, the claims are directed to methods of inhibiting a protein-protein interaction in a host, e.g., for therapeutic purposes. In particular, please the clams recite that the "bifunctional inhibitor molecule is capable of simultaneously binding said target protein (T) and said blocking protein (B) to produce a tripartite complex (T-I-B) that **prevents access of the binding protein (P) to the target protein (T)".**

For example, the invention is directed to methods of inhibiting a biochemical event caused by two proteins, e.g., a target protein and an effector protein (which effector protein is referred to as a binding protein in the claims), by inhibiting the binding of the binding protein to the target protein. The targeted binding event between a target protein and a binding protein that is the subject of the subject methods is illustrated below:

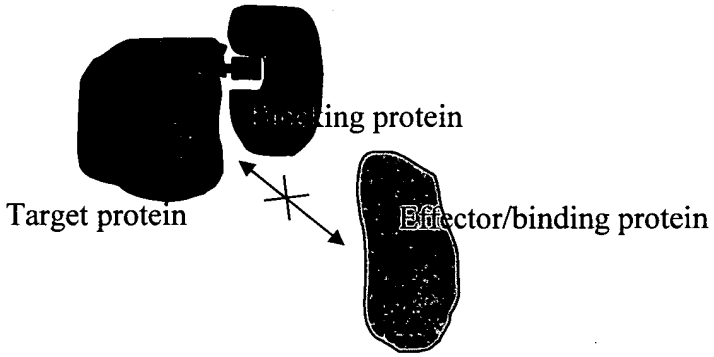


Traditionally, inhibition of such an interaction was accomplished using inhibitor molecules. However, in the present invention, a bifunctional molecule is used to recruit a blocking protein in vivo to produce an inhibiting complex. The bifunctional molecule is made up

of target protein ligand and a second ligand that binds to a blocking protein. A representation of the bifunctional molecules employed in the subject invention is provided below:



When administered to the host, the bifunctional molecule binds to the target protein and a blocking protein, thereby inhibiting binding of the binding protein to the target. This process of simultaneously and non-covalently binding to the target protein and the blocking protein and thereby inhibiting binding of the binding protein (e.g., effector protein) to the target is illustrated below:



As the bifunctional ligand is a small molecule, i.e., less than 5000 daltons, that nonetheless turns into an effective inhibitor complex when it binds to the blocking protein, it satisfies the above need felt in the field of pharmaceutical inhibitor active agents.

In contrast, Briesewitz et al. discloses bifunctional molecules created by linking a ligand for a target protein and a ligand for a binding protein, wherein the ligands bind tightly to the target and binding proteins thereby increasing favorable protein-protein interactions between the target and binding proteins (see abstract, page 1953, see also Fig. 3E, page 1956). The cited reference does not teach use of the bifunctional molecules for the purpose of **recruiting a blocking protein and preventing the interaction between a target protein and an effector/binding protein**.

As such, Briesewitz et al. only teaches or suggests methods in which a bifunctional molecule is used to increase the favorable protein-protein interactions between a target protein and binding protein. The cited reference does not teach the recruitment of a blocking protein that prevents the interaction between the target protein and the binding protein.

Therefore, since the cited reference fails to teach each and every element of the claims, the cited reference fails to anticipate the claims under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-166.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Oct. 24, 2006

By: _____
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Enclosure:

- Exhibit A: Gestwicki et al., Science 306:865-869 (2004)

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